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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/943,664	08/30/2001	David Botstein	P2548P1C8	2448

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EXAMINER	
O HARA, EILEEN B	
ART UNIT	PAPER NUMBER
1646	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/07/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/943,664	BOTSTEIN ET AL.	
	Examiner	Art Unit	
	Lorraine Spector, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 December 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *27-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 August 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/11/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims Status

Claims 27-34 are pending in the instant application. No claim was amended in the response filed 12/11/2006.

Claim Rejections - 35 USC §§ 101 and 112

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 27-34 remain rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

Claims 27-34 also remain rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

The basis for these rejections is set forth at pp. 3-7 of previous Office Action (Paper mailed March 24, 2003), at pp. 3-6 of Paper mailed Sept. 24, 2003, at pp. 3-14 of the Paper Mailed March 17, 2005, Paper mailed Sept. 20, 2005 at pages 3-8, Paper mailed January 24, 2005, and below.

Applicant's arguments (pp. 4-18, Paper filed December 11, 2006) have been fully considered but are not found to be persuasive for the following reasons. Applicant reviews the legal standard for patentable utility, with which the examiner takes no issue.

To review prosecution briefly, the Examiner has made a prima *facie case* that the mild

amount of gene amplification (approximately 2 fold to 4 fold) of nucleic acids encoding the claimed protein are not indicative of an increased amount of protein. It is noted that the data are drawn only to the comparison of genomic DNA. There is no disclosure of mRNA levels. Thus, the issue here is not whether the expression levels based upon DNA were significantly different in the tested tumors, but rather whether this data makes it more likely than not that the protein encoded by the gene is overexpressed.

The major issue in this rejection is that determination of genomic DNA amplification of 2-4 fold universal normal control does not render it predictable that the PRO347 *mRNA* is expressed at a significantly higher level in colon tumors vs. normal colon tissue, and that that elevated mRNA level, were it observed, would result in a similar disparity in protein levels, and hence confer utility to the claimed polypeptides. In the response filed 12/11/2006, applicants have cited no fewer than 146 newly submitted references in support of their position that mRNA levels are predictive of protein. In reality, while some of the submitted references support applicants case, many do not, either because the methodology therein is not comparable to that used by applicants, or because the genes in question were pre-identified as being overexpressed in cancer, and the mRNA was only examined retrospectively, or various other reasons. The mere existence of 146 references that do not provide consistent teachings to support applicants case is evidence of the unpredictability in the art, the type of unpredictability that leads to the conclusion that the instant specification represents a mere invitation to experiment to determine a utility for the claimed protein.

At at pages 5-6, applicants reiterate their discussion of the two Polakis declarations. Thess declarations were considered in previous Office Actions. While maintaining that the Polakis II declaration is not pertinent, the examiner offers the following observations pertaining to it, due to applicant's continued argument:

In assessing the weight to be given expert testimony, the examiner may properly consider, among other things, the nature of the fact sought to be established, the strength of any opposing evidence, the interest of the expert in the outcome of the case, and the presence or absence of factual support for the expert's opinion. See Ex parte Simpson, 61 USPQ2d 1009 (BPAI 2001), Cf. Redac Int'l. Ltd. v. Lotus Development Corp., 81 F.3d 1576, 38 USPQ2d 1665

(Fed. Cir. 1996), Paragon Podiatry Lab., Inc. v. KLM Lab., Inc., 948 F.2d 1182, 25 USPQ2d 1561, (Fed. Cir. 1993).

Affidavits or declarations are provided as evidence and must set forth facts, not merely conclusions. In re Pike and Morris, 84 USPQ 235 (CCPA 1949).

The Polakis II declaration has been fully considered to the following effect:

In the instant case, the nature of the fact sought to be established is whether or not comparison of mRNA in a tumor tissue to that in a universal normal control increased protein levels in cancerous versus normal tissue *of the same tissue type*. Dr. Polakis declares that 28 of 31 genes identified as being detectably over expressed at the mRNA level were found also to have increased protein levels. Therefore, the declaration does not address the most pertinent fact to be established; without knowing whether the PRO347 mRNA is overexpressed in colon tumors vs. normal colon tissue, the issue of predictability of protein on the basis of mRNA is moot. It remains that the only data on the record pertain to DNA levels, and not mRNA. (2) Regarding the interest of the expert in the outcome of the case, it is noted that Dr. Polakis is employed by the assignee. (3) Finally, Dr. Polakis refers to facts; however, the data refer to the mRNA's in question only by UNQ numbers; it is not clear whether PRO347 is represented, and declarant provides no information about the sequences that *are* represented; the assertion in the specification is that PRO347 is overexpressed in colon tumors. Further, the universal control is not described as comprising *any* breast or colon tissue. There is no indication of *how much* the mRNA and protein were overexpressed, as there is no actual description of the experiment that was done, but rather a conclusory statement as to what was measured, and what it means.

For the reasons above, the Polakis II declaration is not sufficient to overcome the rejection of the claims under 35 U.S.C. §101 and §112, first paragraph.

The Examiner notes that the two Polakis declarations are not consistent:

In the first declaration, Dr. Polakis declares that "we have identified approximately 200 gene transcripts that are present in human tumor cells at significantly higher levels than in corresponding normal human cells". In the second, he states that "we have identified

approximately 200 gene transcripts that are present in human tumor ***tissue*** at significantly higher levels than in corresponding normal human ***tissue***."

In the first declaration, Dr. Polakis declares that "In approximately 80% of our observations we have found that increases in the level of a particular mRNA correlates with changes in the level of protein expressed from that mRNA when human tumor cells are compared with their corresponding normal cells." In the second, he states that "of the 31 genes identified as being detectably overexpressed in human tumor tissue as compared to normal human tissue at the mRNA level, 28 of them (i.e. greater than 90%) are also detectably overexpressed in human tumor tissue as compared to normal human tissue at the protein level."

It cannot be determined whether the two declarations are referring to the same data set, or different data sets. Further, there has been no explanation of why the Declarant now refers to tumor *tissue* rather than tumor *cells,* nor what the perceived significance of this change is.

At page 7 of the response, applicants discuss the Scott declaration. Applicant argues that Dr. Scott, an eminent researcher in this field, is of the opinion that mRNA levels correlate with protein levels. The Scott declaration under 37 CFR 1.132 filed 16 November 2006 is insufficient to overcome the rejection of the claims based upon 35 U.S.C. §§ 101 and 112, first paragraph for the following reasons. In assessing the weight to be given expert testimony, the examiner may properly consider, among other things, (1) the nature of the fact sought to be established, (2) the strength of any opposing evidence, (3) the interest of the expert in the outcome of the case, and (4) the presence or absence of factual support for the expert's opinion. See Ex parte Simpson, 61 USPQ2d 1009 (BPAI 2001), Cf. Redac Int'l. Ltd. v. Lotus Development Corp., 81 F.3d 1576, 38 USPQ2d 1665 (Fed. Cir. 1996), Paragon Podiatry Lab., Inc. v. KLM Lab., Inc., 948 F.2d 1182, 25 USPQ2d 1561, (Fed. Cir. 1993). In the instant case, (1) the nature of the fact sought to be established is whether or not mRNA levels are predictive of polypeptide levels in a sample. (2) The opposing evidence, cited by the examiner, is considerably strong. Please see the numerous references cited above. (3) Dr. Scott does not appear to have an interest in the outcome of the case. (4) Finally, the Dr. Scott does not base his opinion on any particular facts other than his own considerable experience in the field. Affidavits or declarations are provided as evidence

and must set forth facts, not merely conclusions. In re Pike and Morris, 84 USPQ 235 (CCPA 1949). While the declaration constitutes evidence that must be considered, there is also other evidence that mRNA levels are not predictive of polypeptide levels. The mere volume of contradictory publications on this topic speaks to the unpredictability of the issue. Also, there remains the primary issue of the universal normal control used in the microarray assay of this specification. Thus, consideration of the preponderance of the totality of the evidence indicates that the rejections should be maintained.

In the Response of 12/11/2006, Applicant has submitted teachings from Alberts, B. (Molecular Biology of the Cell (3rd ed 1994 and 4th ed 2002)) and Lewin, B. (Genes VI 1997) to support the statements of Dr. Polakis (Polakis II declaration; (see above). Applicant also cites numerous references to emphasize that those of skill in the art would not be focusing on differences in gene expression between cancer cells and normal cells if there were no correlation between gene expression and protein expression (such as Zhigang et al., Meric et al. Orntoft et al., Wang et al., Munaut et al., Hui, Khal, etc.). Applicant asserts that changes in mRNA level generally lead to corresponding changes in the level of expressed protein. Applicant also contends that the references and the Polakis declaration establish that the accepted understanding in the art is that there is a reasonable correlation between changes in gene expression and the level of the encoded protein.

Applicant's arguments have been fully considered but are not found to be persuasive. While the Examiner acknowledges the teachings of Alberts and Lewin, which disclose that initiation of transcription is the most common point for a cell to regulate the gene expression, it is not the only means of regulating gene expression. For example, Alberts also teaches that there are a number of other controls that can act later in the pathway from RNA to protein to modulate the amount of protein that is made, including translational control mechanisms and mRNA degradation control mechanisms (see Alberts 3rd ed., bottom of pg 453). Meric et al. states the following:

"The fundamental principle of molecular therapeutics in cancer is to exploit the differences in gene expression between cancer cells and normal cells. [M]ost efforts have concentrated on identifying differences in gene expression at the level or mRNA, which can be attributable to either DNA amplification or to differences in transcription."

However, Meric et al. also goes on to state that gene expression is quite complicated, and is also regulated at the level of mRNA stability, mRNA translation, and protein stability (see page 971, Introduction). Meric et al. also teaches that there are a number of translation alterations encountered in cancer, including variations in the mRNA sequence as a result of mutations, alternate splicing and transcription start sites, alternate polyadenylation sites, and alterations in the components of the translation machinery (see pages 973-974). Celis et al. also teach that "[g]enes may be present, they may be mutated, but they are not necessarily transcribed. Some messengers are transcribed but not translated, and the number of mRNA copies does not necessarily reflect the number of functional protein molecules" (pg 6, col 2).

Furthermore, it would appear that most or all of Applicant's newly cited references (with the exception of Orntoft et al.) measure mRNA and make no correlation between the amount of mRNA observed and the number of copies of genomic DNA. Also, with the exception of Futcher et al., all of Applicant's newly cited references are directed to the analysis of single genes, or a small group of genes, and therefore do not demonstrate trends found across proteins in general. The studies cited by Applicant that examine the expression of specific genes or small numbers of genes are not found persuasive in view of comprehensive studies where significantly larger numbers of transcripts and proteins were examined and more accurately describe general trends, specifically, Haynes (80 proteins examined).

Additionally, the majority of the newly cited references by Applicants are drawn to genes known or suspected to be over expressed or under expressed in cancers, and encode proteins that are involved with cell proliferation, differentiation and/or cell adhesion/migration, in which expression of the proteins are important in the development and progression of the cancer. For example, Wang et al. (discussed at page 10 of the response) analyzes expression of the cadherins, which are a family of transmembrane proteins that play a crucial role in cell differentiation, cell migration, and intercellular adhesion. Down-regulation of E-cadherin protein had been shown in various human cancers. Wang et al. states: "In conclusion, this paper presents a coordinated down-regulation in the expression of E-cadherin and associated catenins at the mRNA and protein level in most of the cases studied. This down-regulation may play an important role in

the pathogenesis of prostate cancer." Note that the protein had been pre-selected as being known to be associated with human tumors, which is not true for PRO347.

All of the references discussed by applicants at pages 10-14, with the single exception of the Godbout reference, are drawn solely to the issue of predictability of protein on the basis of mRNA levels. However, in this application, NO mRNA OR protein levels have been measured. Therefore, the probative issue, based upon the evidence of record is whether or not an increase of 2-4-fold at the DNA level in unspecified colon tissue as compared to a "universal normal control" that contains no colon tissue would be predictive of overexpression of PRO347 protein. The Examiner maintains the previous argument of record, namely that mRNA levels are not necessarily predictive of protein levels. Regarding Applicants' arguments that a change in mRNA expression level leads to a corresponding change in the level of expression of the encoded protein, the specification of the instant application does not teach a change in mRNA level of PRO347. The specification simply discloses a static measurement of PRO347 DNA in colon tumor as compared to "normal". Upon re-reading the example in the specification, the Examiner finds that the "normal" control seems to be human blood; therefore, the comparison is not even between normal *colon* tissue and colon tumor, but may, in fact be a comparison to blood, an unrelated tissue. There are no teachings in the specification as to the differential expression of PRO1564 mRNA in the progression of any type of tumors, nor disclosure of what specific type of tumor(s) was or were tested. (Note that a "colon" tumor is a tumor found in the lung; it does not disclose what the tissue type of the originating cells were, nor does it distinguish a primary tumor from a metastasis, which might have originally arisen in a different part of the body.) Therefore, the Examiner maintains that Applicant's measurement of an increase of PRO1564 DNA as compared to a control, possibly from a different type of tissue, does not provide a specific and substantial utility for the encoded protein.

While the vast majority of newly cited references are drawn to predictability of protein on the basis of mRNA amplification (and for reasons cited above do not merit further discussion), a single reference, that by Godbout, is pertinent to the issue at hand. However, the Examiner finds applicants interpretation of the reference to be erroneous. Far from teaching predictability for expression of PRO347 on the basis of a minor genomic amplification, Godbout teaches "The

DEAD box gene, DDX1, is a putative RNA helicase that is co-amplified with MYCN in a subset of retinoblastoma (RB) and neuroblastoma (NB) tumors and cell lines. Although gene amplification usually involves hundreds to thousands of kilobase pairs of DNA, a number of studies suggest that co-amplified genes are only overexpressed if they provide a selective advantage to the cells in which they are amplified." The protein encoded by the DDX gene *had been characterized* as being a putative RNA helicase, a type of enzyme that *would be expected to confer a selective advantage* to the cells in which it (the DDX gene) was amplified. That result was (apparently, applicants only having submitted the abstract) confirmed. On the contrary, there is no structure/function analysis in the specification regarding the putative protein encoded by the PRO347 gene. It is not disclosed, and based upon the sequence searches in this case, the Examiner can not find any reason to suspect, that the protein encoded by the PRO347 gene would confer any selective advantage on a cell expressing it. It has no known homology to an RNA helicase or any other protein that would be expected to confer a selective advantage to a tumor cell. Further, it cannot be determined from the abstract whether the level of genomic amplification of the DDX1 gene was comparable to that disclosed for PRO347.

In summary, of applicants 146 references submitted, only a single one, Godbout, is drawn to the predictability of protein levels based upon genomic DNA amplification, and that one supports the Examiners assertion that it is more likely than not that the PRO347 protein would *not* be expected to be found in increased amounts in the cells tested by applicants, and thus has no utility as a cancer diagnostic. It remains that the specification merely finds modest amplification of the PRO347 gene (DNA) in *some* of the colon tumors tested, that it is not clear whether that determination was made by comparison to normal colon tissue or to blood, that aneuploidy, or the duplication of chromosomes or portions thereof is known to be associated with cancer (see Godbout, for example), and despite that, that the amplified genes would not be expected to be over-expressed *a priori*, in the absence of any reason to expect that additional PRO347 protein would confer a selective advantages to tumor cells (op. cit.) Accordingly, the Examiner maintains the conclusion that it is more likely than not that the PRO347 protein would *not* be expected to be found in increased amounts in the cells tested by applicants, and thus has no readily available utility as a cancer diagnostic.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eileen B. O'Hara, whose telephone number is (571) 272-0878. The examiner can normally be reached on Monday through Friday from 10:00 AM to 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol can be reached at (571) 272-0835.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://portal.uspto.gov/external/portal/pair. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Eileen B. O'Hara, Ph.D.

Patent Examiner

Lorraine Spector

LORRAINE SPECTOR
PRIMARY EXAMINER